ANTICANCER RESEARCH 10: 971-976 (1990)

Epidemiologic Characteristics and Multiple Risk Factors of Lung Cancer in Taiwan*

CHIEN-JEN CHEN[1,2], HSIN-YING WU[1], YA-CHIEN CHUANG[3], AH-SENG CHANG[2], KUN-TAI LUH[1], HSIO-HSIUNG CHAO[4], KUANG-YAW CHEN[4], SHIN-GON CHEN[5], GI-MING LAI[6], HSIH-HSIN HUANG[7] and HONG-HSIN LEE[5]

[1]*Institute of Public Health, National Taiwan University College of Medicine, Taipei, Taiwan;*
[2]*Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan;*
[3]*Department of Epidemiology, Pittsburgh University School of Public Health, Pittsburgh, Pennsylania, U.S.A.;*
[4]*Veteran General Hospital, Taiepi, Taiwan;*
[5]*Bureau of Public Health, Department of Health, Executive Yuan, Taipei, Taiwan;*
[6]*Chang-Gung Memorial Hospital and Medical College, Taipei, Taiwan;*
[7]*Cathay General Hospital, Taipei, Taiwan*

Abstract. *The specific aim of this study was to examine epidemiologic characteristics and multiple risk factors of lung cancer in Taiwan. The age-adjusted mortality from lung cancer has been increasing since the early 1950s with a constant male-to-female ratio of around 2.0. International comparison of cumulative moratlity from lung cancer showed a much lower male-to-female ratio in Chinese than in other populations. Significantly high moratlity from lung cancer was observed in highly urbanized cities and the endemic area of chronic arsenicism in Taiwan. Significant associations of active and passive cigarette smoking with epidermoid carcinoma, small cell carcinoma and adenocarcinoma of the lung were observed in a hospital - based case - control study carried out in Taipei metropolitan areas. Alcohol drinking, coffee drinking and various types of indoor air pollution were not related to lung cancer after the cigarette smoking habit was adjusted through a multiple logistic regression analysis.*

Lung cancer is one of the most important cancers in Taiwan where malignant neoplasm has become the leading cause of death since 1982. The mortality from lung cancer ranked the second in both men and women among various cancer sites in Taiwan (1). The annual number of deaths from lung cancer was as high as 2,500-3,000 in the 1980s (2). It has resulted in a significant socioeconomic impact with a work-year loss of 12,500 annually (1).

The one-year survival rate of lung cancer patients was reported as less than 20% in Taiwan (3). The early detection of lung cancer by chest X-ray, sputum cytology and / or fiber optic bronchoscopy remains ineffective and inefficient (3-5). Other screening methods, including tumor marker levels, still need further evaluation (6). Primary prevention and intervention become an important task in the control of the disease. The identification of risk factors for lung cancer is essential for an effective and efficient primary prevention.

Both genetic and environmental risk factors have been related to the development of lung cancer. **Risk factors which have been documented include active and passive cigarette smoking**, occupational and environmental exposures to arsenic, asbestos, chromium, mustard gas, radon and polyaromatic hydrocarbons, as well as inadequate consumption of dark green vegetables (7-11). Populations in different areas may have different risk factors for lung cancer, and the same risk factors may be of different importance in different populations and / or areas. The study of risk factors in various populations is important not only for the disease control program, but also for the elucidation of its etiological mechanism.

Although epidemiologic characteristics of lung cancer in Taiwan have been described in two previous reports (12, 13), there has never been a case-control study aimed at elucidating possible risk factors for lung cancer in Taiwan. In this report, we updated the analysis of epidemiologic characteristics of lung cancer mortality and incidence, and examined multiple risk factors for the disease based on a hospital - based matched case - control study.

Materials and Methods

Analysis of mortality and incidence rates. The data on lung cancer deaths

Presented at the Second International Conference of Anticancer Research, October 11-15, 1988, Saronis, Greece.

Correspondence to: Prof. Chien-Jen Chen, Black Building Room 209, Columbia University Comprehensive Cancer Center, 650 West 168th Street, New York, New York 10032, USA.

Key Words: Epidemiology, risk factors, lung cancer.

0250-7005/90 $2.00+.40

Table I: *Secular trend of age-adjusted lung cancer mortality rates per 100,000 population from 1954 to 1988 in Taiwan by sex.*

Year	Age-adjusted mortality		Male-to-female
	Male	Female	ratio
1954-1958	3.88	2.07	1.87
1959-1963	6.49	3.53	1.84
1964-1968	10.35	5.84	1.77
1969-1973	13.97	6.68	2.09
1974-1978	16.65	8.29	2.01
1979-1983	21.79	10.42	2.09
1984-1988	24.91	12.22	2.04

from 1954 to 1988 were obtained from the Taiwan Provincial Department of Health which is in charge of the death certification system in Taiwan. Population data for the same period were abstracted from annual demographic statistics (14). As it is mandatory to register any event of birth, death, marriage, employment and education in household registration offices, mortality data are quite complete and accurate in Taiwan. The incidence of lung cancer in Taiwan was derived from annual reports of national cancer registry (15). As the completeness and accuracy of cancre registry has been assessed in Taipei City only, the incidence data analyzed in this report were limited to those of Taipei City. The mortality from lung cancer in 17 selected countries was obtained from the annual vital statistics published by the World Health Organization (16). Incidence rates of lung cancer among Chinese males and females in San Francisco, Los Angeles, Hawaii, Hong Kong and Shanghai were abstracted from the registration data published by the International Agency for Research on Cancer (17).

In the analysis of mortality and incidence, age-sex-specific rates were first calculated for different areas and / or calendar years. The age was stratified into 15 five-year groups from less than 5 to 70 or more. Age-adjusted mortality and incidence rates were calculated using world population in 1976 (17) as the standard population for the study of secular trend, migrant comparison and geographical variation in Taiwan, while cumulative mortality rates over the age range from 0 to 84 years were for international comparison.

Hospital-based matched case-control study. As most patients suspected of having lung cancer are referred to teaching hospitals for confirmatory diagnosis and treatment in Taiwan, we recruited serial patients with lung cancer from four major teaching hospitals in Taipei City. All patients were newly diagnosed and pathologically confirmed. A total of 354 new cases were recruited and 332 (93.8%) agreed to participate in the study. Hospital controls group-matched with case on hospital, age and sex were recruited from ophthalmic patients of study hospitals with a control-to-case ratio of 3:1. Among 664 recruited controls, 635 (95.6%) of them agreed to participate in the study.

A structured questionnaire was used to obtain socio-demographic characteristics and the history of exposure to risk factors including cigarette smoking, alcohol drinking, tea and coffee drinking, as well as indoor air pollution resulting from burning incense and mosquito coils. The consumption frequency, quantity and duration were inquired for habits of cigarette smoking, alcohol drinking, tea drinking and coffee drinking.

In addition to the questions mentioned above, the interview time and interviewer - assessed reliability of the interviewee's response were also included. The average interview time in minutes was 37.4 and 31.5 respectively for cases and hospital controls. There were 9 (2.7%) cases and 18 (2.8%) controls whose responses were rated as unreliable because of poor memory and / or cooperation. In all, there were 323 cases and 617 hospital controls available for the final analysis. With regard to the pathological type of the 323 lung cancer patients, there were 133 (41.2%) affected with epidermoid carcinoma, 47 (14.6%) with small cell carcinoma, 134 (41.5%) with adenocarcinoma, and 9 (2.8%) with other minor pathological types.

In the univariate analysis, the odds ratio and its statistical significance of each risk factor were assessed for three major pathological types of lung cancer. Mantel - Haenszel chiquare test (18) was used to assess the statistical significance of age-sex-adjusted odds ratios for each risk factor. As several risk factors were inter-correlated, multiple logistic regression analysis (19) was used to estimate multivariate - adjusted odds ratios. In the regression analysis, only significant risk factors observed in the univariate analysis were included in the regression equation. BMDP statistical software was used to estimate regression coefficients through the maximum likelihood method (19).

Results

Secular trend. The secular trend of lung cancer mortality from 1954 to 1988 in Taiwan is shown in Table I. The age - adjusted mortality rate of lung cancer increased strikingly during the period for both males and females; it increased significantly from 3.88 per 100,000 in 1954-1958 to 24.91 per 100,000 in 1984-1988 for males, and from 2.07 per 100,000 in 1954-1958 to 12.22 per 100,000 in 1984-1988 for females. The male-to-female ratio of age-adjusted lung cancer mortality remained around 2.0 during the period from 1954 to 1988.

International comparison, migrant difference and geographical variation. The international comparison of lung cancer mortality in Taiwan and 17 selected countries is shown in Table II. Males in Scotland and The Netherlands had the highest mortality from lung cancer, while males in Taiwan and mainland China had the lowest. Females in Hong Kong and Scotland had the highest mortality, while females in the Netherlands and mainland China had the lowest. The cumulative mortality rate of lung cancer in Taiwan ranked as the 17th and 9th, respectively, for males and females. The male-to-female ratio of the cumulative mortality rate of lung cancer varied significantly from greater than 6.0 in the Netherlands, West Germany and Italy to less than 3.0 in Taiwan, China and Hong Kong.

The comparison of age-adjusted incidence rate of lung cancer among Chinese in different areas is shown in Table III. The rate for males was highest in Singapore and lowest in Taipei, while that for females was highest in San Francisco and lowest in Los Angeles. The male-to-female ratio in age-adjusted mortality from lung cancer ranged from 1.33 in Hawaii to 3.43 in Singapore.

There was also a striking geographical variation of lung cancer mortality among 361 townships and precincts in Taiwan. Generally speaking, males and females had similar geographical variation in age-adjusted mortality of lung cancer with a correlation coefficient of 0.54. High lung cancer mortality was observed in highly urbanized cities as well as in the endemic area of chronic arsenicism, while low mortality was observed in rural townships where aboriginals and Hakka Taiwanese reside. There was a significant correlation in the geographical variations of lung cancer with cancers of the liver, pancreas, bladder and kidney in males and females as

Table II. *Comparison of cumulative mortality from lung cancer in Taiwan and 17 selected countries.*

Rank	Male Country	Male CMR	Female Country	Female CMR
1	Scotland	21.22	Hong Kong	5.95
2	Netherlands	20.04	Scotland	4.40
3	England & Wales	18.61	Singapore	4.37
4	Hong Kong	13.97	England & Wales	3.97
5	Singapore	13.87	USA	3.43
6	Hungary	13.82	Ireland	3.24
7	Austria	13.52	Canada	2.79
8	Canada	13.16	Hungary	2.56
9	USA	13.04	Taiwan	2.52
10	West Germany	12.99	Israel	2.39
11	Australia	12.59	Australia	2.07
12	Italy	11.47	Japan	2.06
13	Ireland	11.05	Austria	2.05
14	Japan	7.38	West Germany	1.56
15	Israel	7.14	Italy	1.48
16	Chile	5.08	Chile	1.45
17	Taiwan	4.98	Netherlands	1.43
18	China	1.95	China	0.93

CMR: Cumulative mortality rates, 0-84 years (percent)

Table III. *Age-adjusted incidence rates per 100.000 population of lung cancer among Chinese in six cities in Asia and USA.*

City	Age-adjusted mortality Male	Age-adjusted mortality Female	Male-to-female ratio
Singapore	68.0	19.8	3.43
San Francisco	57.8	25.1	2.30
Hong Kong	55.5	23.4	2.37
Shanghai	51.2	18.1	2.83
Los Angeles	33.8	13.6	2.49
Hawaii	31.4	23.6	1.33
Taipei	27.7	14.4	1.92

Table IV. *Ecological correlation between age-adjusted mortality rates of lung cancer and other cancers in 361 townkships and precincts in Taiwan.*

Correlation	Male	Female
Lung *vs.* liver	0.17	0.24
Lung *vs.* pancreas	0.29	0.21
Lung *vs.* bladder	0.35	0.74
Lung *vs.* kidney	0.24	0.66
Lung *vs.* prostate	0.29	-

well as with cancer of the prostate in males, as indicated in Table IV.

Case-control study. Table V shows frequency distributions of age and sex of 133 epidermoid carcinoma, 47 small cell carcinoma and 134 adenocarcinoma patients and of 617 ophthalmic hospital controls. They were all comparable in the distribution of age and sex. The age-sex-adjusted odds ratios for cigarette smoking on the development of various pathological types of lung cancer are shown in Table VI. There was a significant association between cigarette smoking and epidermoid carcinoma, small cell carcinoma and adenocarcinoma of the lung, with an odds ratio of 6.66, 3.59 and 2.08, respectively. Futhermore, the duration, quantity and inhalation degree of cigarette smoking were all significantly associated with three pathological types of lung cancer in a dose-response relation. Passive smoking was also correlated with the development of epidermoid carcinoma, small cell carcinoma and adenocarcinoma of the lung with a significant odds ratio of 4.68, 2.55 and 3.04, respectively.

The age-sex-adjusted risk of developing various pathological types of lung cancer for alcohol drinking, tea drinking and coffee drinking are shown in Table VII. Alcohol drinking was significantly associated with epidermoid carcinoma of the lung with an odds ratio of 1.57. Neither small cel carcinoma nor adenocarcinoma was significantly correlated with alcohol drinking. None of the habits of drinking black tea, half-processed tea and green tea was significantly associated with any pathological type of lung cancer. Coffee drinking was found to be associated significantly with epidermoid carcinoma of the lung only.

Table VIII shows associations between various kinds of indoor air pollution and pathological types of lung cancer. Neither burning incense at home nor type of cooking fuels was related to the development of any type of lung cancer. Burning mosquito coils at home was found to be significantly associated with the development of epidermoid carcinoma and adenocarcinoma of the lung, with an odds ratio of 1.81 and 1.70, respectively.

As risk factors significantly associated with various pathological types of lung cancer were inter-correlated, a multiple logistic regression analysis was empolyed to assess multivariate - adjusted odds ratio for various variables. Separate regression analysis was carried out for each pathological type of lung cancer. Only active and passive cigarette smoking were significantly associated with the three pathological types of lung cancer. Alcohol drinking, coffee drinking and burning mosquito coils at home were not significantly associated with any pathological type of lung cancer after cigarette smoking was adjusted.

Discussion

Increasing secular trend and significant geographical variation are two interesting epidemiologic characteristics of lung cancer. This suggests the importance of environmental factors in the determination of the disease. In this study, we observed an increase in lung cancer mortality in Taiwan since the early 1950s. The result is consistent with those observed in most countries (20). The increas in age-adjusted lung cancer mortality in Taiwan may be attributable to improved diagnostic methods, increased consumption of cigarettes,

Table V. *Age and sex distributions of 133 epidermoid carcinoma, 47 small cell carcinoma, and 134 adnocarcinoma patients and 617 opthalmic hospital controls in metropolitan Taipei areas.*

Variable	Group	Epidermoid carcinoma No. (%)	Small cell carcinoma No. (%)	Adeno-carcinoma No. (%)	Hospital controls No. (%)
Age	< 55	21 (15.8)	17 (36.2)	38 (28.4)	146 (23.7)
	55-64	59 (44.4)	14 (29.8)	50 (37.3)	244 (39.5)
	65 +	53 (39.8)	16 (34.0)	46 (34.3)	227 (36.8)
Sex	Male	111 (83.5)	36 (76.6)	101 (75.4)	488 (79.1)
	Female	22 (16.5)	11 (23.4)	33 (23.4)	129 (20.9)

Table VI. *Age-sex-adjusted odds ratios for cigarette smoking on the development of three pathological types of lung cancer.*

Variable	Group	Age-sex-adjusted odds ratio		
		Epidermoid carcinoma	Small cell carcinoma	Adeno-carcinoma
Habit	Yes	6.66***	3.59***	2.08***
	No	1.00	1.00	1.00
Duration (year)	41+	8.43***	5.12***	3.79***
	31-40	6.52	4.30	1.60
	21-30	2.76	3.33	1.52
	1-20	1.70	2.16	1.23
	None	1.00	1.00	1.00
Quantity (cig./day)	31+	11.11***	8.09***	3.61***
	21-30	7.61	4.64	2.34
	11-20	7.05	3.48	1.74
	1-10	2.59	2.45	1.21
	None	1.00	1.00	1.00
Inhalation	Deep	7.23***	4.37**	2.21*
	Shallow	3.67	3.57	1.92
	None	1.00	1.00	1.00
Passive smoking	Yes	4.68*	2.55*	3.04*
	No	1.00	1.00	1.00

* $p < 0.05$, ** $p < 0.01$, *** < 0.001 based on Mantel - Haenszel chi-square tests.

Table VII. *Age-sex-adjusted odds ratios for beverage drinking on the development of three pathological types of lung cancer.*

Variable	Group	Age-sex-adjusted odds ratio		
		Epidermoid carcinoma	Small cell carcinoma	Adeno-carcinoma
Alcohol drinking				
Habit	Yes	1.57*	1.36	1.17
	No	1.00	1.00	1.00
Frequency (days/week)	4+	1.72*	1.90	1.50
	1-3	1.43	0.90	0.98
	None	1.00	1.00	1.00
Tea drinking				
Black tea	Yes	0.20	1.10	0.19
	No	1.00	1.00	1.00
Half-processed tea	Yes	1.52	0.99	0.99
	No	1.00	1.00	1.00
Green tea	Yes	1.48	1.20	1.77
	No	1.00	1.00	1.00
Coffee drinking	Yes	2.10*	1.44	1.25
	No	1.00	1.00	1.00

* $P < 0.05$ based on Mantel - Haenszel chi-square tests

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Table VIII. *Age-sex-adjusted odds ratios for various types of indoor air pollution on the development of three pathological types of lung cancer.*

Variable	Group	Age-sex-adjusted odds ratio		
		Epidermoid carcinoma	Small cell carcinoma	Adeno-carcinoma
Burning incense	Yes	0.77	1.33	0.99
	No	1.00	1.00	1.00
Burning mosquito coils	Yes	1.81*	1.13	1.70*
	No	1.00	1.00	1.00
Cooking fuels	Wood & coal	0.85	1.08	1.02
	Charcoal, gas & electricity	1.00	1.00	1.00

$p < 0.05$ based on Mantel - Haenszel chi - square tests.

rapid industrialization and urbanization, and worsened air pollution. International comparison of cumulative mortality from lung cancer revealed a striking difference in the male-to-female ratio among 18 countries studies. The reason for a much lower male-to-female ratio among Chinese in various countries deserves further investigation. As most Chinese women are non-smokers and 60% of female lung cancer patients are affected with adenocarcinoma (12), it seems reasonable to suspect that risk factors other than active cigarette smoking are involved in the development of adnocarcinoma. The striking geographical variation in lung cancer mortality among 361 townships and precincts in Taiwan also suggests the importance of environmental factors. Heavy air pollution resulting from urbanization and industrialization may at least partly contribute to the high mortality from lung cancer in cities. Consumption of high-arsenic artesian well water has been documented to be the major risk factor for lung cancer in the endemic area of chronic arsenicism (21). The significant ecological correlation between mortality rates of lung cancer and pancreas cancer may be explained by the better dignosis of the latter in urbanized areas. However, the similar geographical variation in mortality from cancers of the lung, liver, bladder, kidney and prostate may be attributable to their associations with arsenic exposure from drinking water.

In our case-control study, both active and passive cigarette smoking were significantly associated with the development of three pathological types of lung cancer. Almost all epidemiological studies and animal experiments consistently show a significant association between cigarette smoking and lung cancer (7-9, 22). Both epidermoid carcinoma and small cell carcinoma had a stronger association with active cigarette smoking than adenocarcinoma in this study. This observation is consistent with those reported previously. However, there was no difference in the association with passive cigarette smoking for the three pathological types of lung cancer. Futher investigations are needed to explain such a discrepancy.

Habits of alcohol drinking and coffee drinking were significantly associated with the development of epidermoid carcinoma of the lung in the univariate analysis in this study. However, the association was no longer significant after further adjustment for the effect of cigarette smoking. Indoor air pollution has been documented to cause lung cancer in Yunnan Province of China (10). In this study, an effort was made to assess the effects of various types of indoor air pollution on the development of lung cancer. Although a significant association between lung cancer and burning mosquito coils at home was observed in the univariate analysis, it became not significant after active and passive cigarette smoking were adjusted for. The reduction of cigarette smoking through public education remains the most important task for the primary prevention of lung cancer.

Acknowledgements

This study was supported by a grant from the Department of Health, Executive Yuan, Republic of China. Dr. C.J. Chen is a Fogarty Research Fellow sponsored by the US National Institutes of Health.

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Received February 28, 1990
Accepted April 18, 1990